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CASE STUDY

Seronegative Immune-Mediated Necrotizing Myopathy Presenting as Acute Onset Quadriparesis

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ABSTRACT

Immune-mediated necrotizing myopathy (IMNM) is a rare, rapidly progressive inflammatory myopathy that closely resemble Guillain-Barré syndrome (GBS), making early diagnosis particularly challenging. We report the case of a 32-year-old man who initially presented with a five-day history of fever and diffuse body aches, followed by rapidly progressive-,ascending-,symmetrical limb weakness in the lower limbs with progression to the upper limbs. A neurological examination revealed hypotonia with preserved deep tendon reflexes. Sensory, cranial, and cerebellar functions were intact. Given the acute, flaccid nature of the paralysis, GBS was initially suspected; however, cerebrospinal fluid analysis showed no albuminocytologic dissociation. Significantly elevated serum creatine phosphokinase levels, along with persistent myalgia, shifted the clinical suspicion toward a myopathic process. Magnetic resonance imaging (MRI) revealed diffuse-, symmetric hyperintensities in multiple muscle groups, and muscle biopsy confirmed the diagnosis of necrotizing myopathy. Despite extensive autoimmune workup, including myositis-specific antibodies, all results were negative, classifying the condition as seronegative IMNM. The patient responded promptly to high-dose intravenous corticosteroids, followed by oral methotrexate and maintenance oral steroids with recovery at the one-month follow-up. This case highlights the importance of considering IMNM in patients presenting with acute flaccid paralysis and preserved reflexes, as timely diagnosis and early initiation of immunosuppressive therapy are crucial for achieving favorable outcomes.

Keywords: Acute quadriparesis, immune-mediated necrotizing myopathy, Seronegative.

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1. Introduction

Immune-mediated necrotizing myopathy (IMNM) is a distinct subtype of idiopathic inflammatory myopathy (IIMs), a heterogeneous group of disorders characterized by inflammation of skeletal muscles and associated tissues. IMNM most commonly affects women aged 40–60 years and is histologically defined by prominent muscle fiber necrosis [1] on biopsy with minimal inflammatory cell infiltrate. They are frequently associated with specific myositis-specific autoantibodies (MSAs). Based on antibody profiles, IMNM can be categorized into three main subtypes [2]:

1. Anti-signal recognition particle (SRP) myopathy
2. Anti-3-hydroxy-3-methylglutaryl-coenzyme (HMGCR; a reductase) myopathy
3. Seronegative IMNM

It's clinical presentation often mimics that of limb-girdle muscular dystrophy (LGMD), leading to diagnostic challenges.

2. Case Report

A 32-year-old man with no prior co-morbidities, no history of any drug or toxin exposure, presented with a five-day history of fever and generalized body aches, followed by rapidly progressive, symmetrical limb weakness

affecting both upper and lower extremities over the subsequent three days. Weakness initially began in the lower limbs and ascended to involve the upper limbs. No sensory disturbances, cranial nerve involvement, autonomic dysfunction, or cerebellar symptoms were observed.

Neurological examination revealed hypotonia and proximal-predominant muscle weakness, with Medical Research Council (MRC) grades of 3/5 in the neck, 4/5 in the upper limbs, and 3/5 in the lower limbs. The deep tendon reflexes were preserved. No sensory deficits, cranial nerve abnormalities, or cerebellar signs were noted. Given the acute onset of flaccid quadriparesis with preserved reflexes, Guillain-Barré syndrome (GBS) was initially suspected. However, analysis of cerebrospinal fluid (CSF) revealed no albuminocytologic dissociation, prompting reconsideration of the diagnosis.

Laboratory investigations revealed marked leukocytosis (23,000/μL), significantly elevated liver enzymes (AST: 2,566 U/L; ALT: 536 U/L), elevated lactate dehydrogenase (LDH: 5,070 U/L), and an extremely high creatine phosphokinase (CPK) level (151,389 U/L), strongly suggesting a myopathic process. Infectious myositis was considered, and empirical antibiotics (ceftriaxone and vancomycin) were initiated. Despite this, the patient's muscle weakness progressed, with upper limb power declining to 2/5 and lower limb power declining to 1/5, accompanied by worsening myalgia.

Given the lack of response to antibiotics and the clinical deterioration, high-dose pulse methylprednisolone therapy was initiated. By the third day of corticosteroid treatment, the patient's fever and myalgia had markedly improved, and his CPK level had decreased to 27,862 U/L. He was switched to maintenance therapy with oral prednisolone at a dose of 1 mg/kg/day.

Whole-body short tau inversion recovery (STIR) magnetic resonance imaging (MRI) revealed diffuse, symmetric hyperintensities in the muscles of the upper and lower limbs and torso, along with associated subcutaneous edema (Fig. 1). A comprehensive autoimmune panel, including antinuclear antibody (ANA) testing and MSAs (Jo-1, Mi-2, PM-Scl 100/70, U1snRNP, Ku, PL-7, PL-12, EJ, OJ, and Ro-52), was negative. Screening for HIV, hepatitis B and C, and thyroid dysfunction was unremarkable.

A biopsy of the left rectus femoris revealed extensive muscle fiber necrosis (Fig. 2), fibrosis, infiltration by foamy macrophages, overexpression of HLA class I molecules, and sparse lymphocytic infiltration. These findings are consistent with those of necrotizing autoimmune myopathy (Figs. 3 and 4). Moreover, aerobic and, anaerobic cultures of the muscle biopsy were negative for growth of any organism, thus ruling out infectious causes of myositis. Both anti-HMGCR and anti-SRP antibodies were negative, confirming a diagnosis of seronegative immune-mediated necrotizing myopathy.

Given the established association between seronegative IMNM and malignancy, a whole-body CT scan was performed, but showed no evidence of malignancy. Owing to the severity of the disease, methotrexate was initiated at 15 mg/week. The patient showed a significant clinical improvement. Within two weeks, his CPK level normalized to 66 U/L, and corticosteroids were gradually tapered. By the time of discharge, muscle strength had improved to 3/5 in all the major muscle groups. At one-month follow-up, he had made a full recovery, regaining normal strength and independent ambulation with no residual neurological deficits.

3. Discussion

IMNM is a rare subtype of IIM, with an incidence of 8.3 per million person-years reported between 2010 and 2019 [3]. Clinically, IMNM is characterized by rapid or subacute onset of severe proximal muscle weakness and significantly elevated muscle enzyme levels, often with creatine kinase (CK) values exceeding 10 times the upper limit of normal. Among the IIMs, patients with IMNM typically present with the highest serum CK levels.

The precise etiology of IMNM remains unclear; however, genetic and environmental factors have been implicated in its pathogenesis. A strong association exists between HLA-DRB1∗11:01 allele and anti-HMGCR myopathy, particularly in adults. Statin exposure is a well-documented risk factor for anti-HMGCR myopathy, potentially due to the upregulation of HMGCR expression and the subsequent generation of neoantigens. Viral infections have also been implicated as a potential trigger.

Although IMNM is primarily a muscle-limited disorder, extra muscular manifestations may also occur. Interstitial lung disease (ILD) is observed in approximately 10%–20% of patients with anti-SRP antibodies and in less than 5% of those with anti-HMGCR antibodies. Skin involvement is rare, reported in less than 10% of cases of both subtypes. Notably, seronegative IMNM is associated with a significantly increased risk of malignancy, making oncologic evaluation a key component of workup [4].

Although muscle MRI lacks diagnostic specificity for IMNM, it remains a valuable tool for assessing disease extent, monitoring progression, and evaluating therapeutic response. In general, MRI shows more extensive muscle involvement compared than in dermatomyositis or polymyositis. Anti-SRP myopathy tends to exhibit greater muscle atrophy, fatty replacement, and edema [5]. Importantly, studies have demonstrated that fatty muscle replacement may begin early in the course of the disease, underscoring the need for prompt and aggressive immunosuppressive treatment to reduce long-term morbidity.

Histopathologically, IMNM is characterized by necrotic and regenerating muscle fibers, infiltration by CD68+ macrophages, and overexpression of MHC class I molecules. Deposition of the membrane attack complex (MAC) is often observed in non-necrotic fibers. In contrast to dermatomyositis and polymyositis, perifascicular atrophy and primary inflammation—such as lymphocytic invasion of intact fibers—are rarely present, particularly in IMNM [6]. Inflammation is minimal, especially in seronegative cases, which reinforces the necrotizing pathology of this disease.

Despite immunosuppressive therapy, the prognosis of IMNM is less favorable than that compared of other inflammatory myopathies. Studies report that approximately 50% of patients with anti-SRP or anti-HMGCR myopathy have persistent muscle weakness after two years

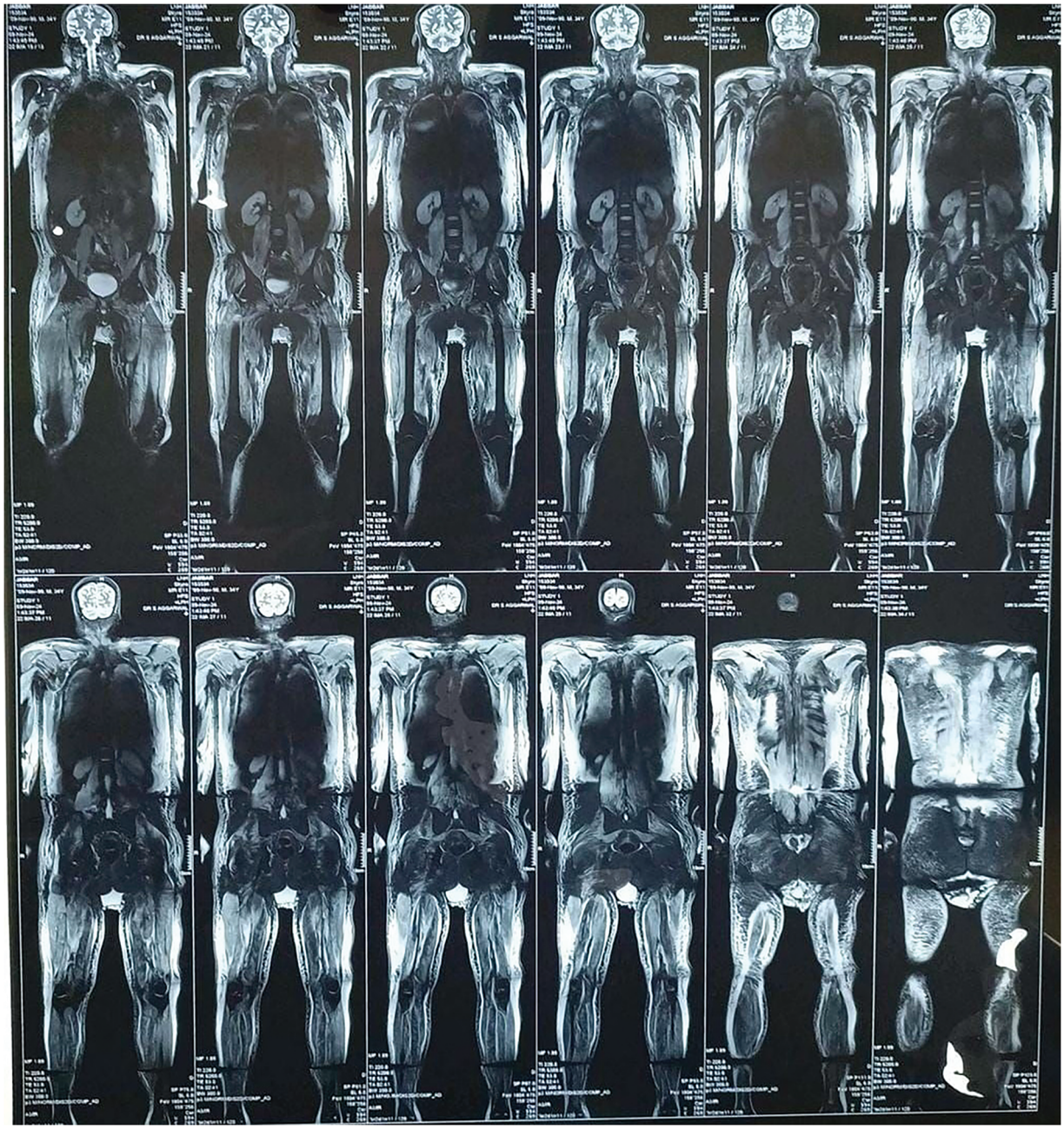

Fig. 1. MRI whole body STIR sequence showing symmetric STIR hyperintensity in all the muscles of the body with diffuse subcutaneous edema.

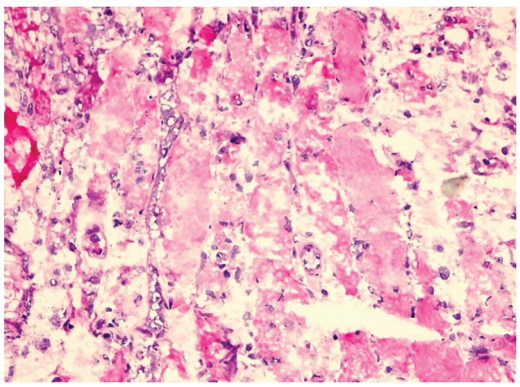

Fig. 2. 20 X image H & E shows necrotic muscle fibres with minimal inflammatory infiltrates.

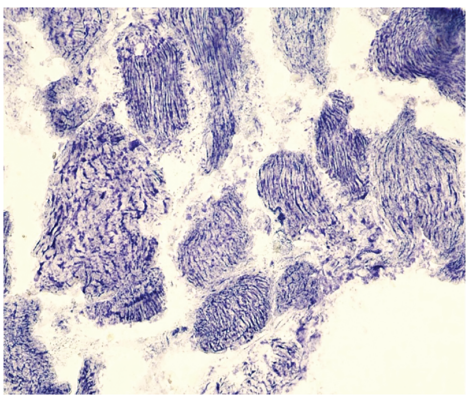

Fig. 3. 40 X LM image: SDH (succinate dehydrogenase) staining shows maintained myofibrillary architecture.

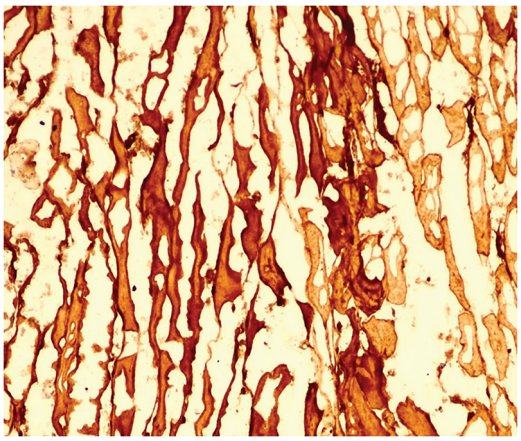

Fig. 4. 20 X image IHC shows diffuse sarcolemmal HLA 1 upregulation.

of treatment. Younger patients appear to have a worse prognosis, possibly because of a more aggressive disease phenotype, than older individuals.

Reports of seronegative IMNM are rare, highlighting its low prevalence and variable clinical presentation. Patel *et al*. [7] described a 61-year-old woman on statin therapy who presented with a five-month history of proximal lower limb weakness. Despite negative myositis-specific antibody results, the patient responded well to methylprednisolone, with subsequent tapering and initiation of azathioprine, with gradual improvement. Similarly, Malladi *et al*. [8] reported on a 38-year-old woman with a one-month history of diffuse pain and fatigue, which was later complicated by myopericarditis. Muscle biopsy confirmed necrotizing myopathy, and she responded to corticosteroids, intravenous immunoglobulin (IVIG), and rituximab over three months. In another case, Bingham *et al*. [9] described a 19-year-old woman with progressive limb and bulbar weakness for over one year. Despite seronegative myositis panels, a muscle biopsy confirmed necrotizing myopathy, and treatment with steroids, mycophenolate mofetil, and IVIG yielded clinical improvement.

All three patients demonstrated a subacute to chronic disease course with delayed onset of weakness, in contrast to our patient, who experienced acute onset, rapidly progressive, and clinically disabling muscle weakness.

The current consensus from the European Neuromuscular Center (ENMC) recommends initiating treatment with corticosteroids in combination with methotrexate. Alternatives include azathioprine, mycophenolate mofetil, tacrolimus, cyclosporine, and cyclophosphamide-However, comparative data on their efficacy remain limited [10]. Rituximab is considered a second-line agent, particularly for patients with anti-SRP myopathy who are unresponsive to initial therapy. IVIG has shown promise in anti-HMGCR myopathy, especially in refractory cases or when corticosteroids are contraindicated. Emerging evidence supports IVIG monotherapy in select patients.

4. Conclusion

This case highlights a rare presentation of seronegative immune-mediated necrotizing myopathy manifesting as acute flaccid quadriparesis, mimicking Guillain-Barré syndrome. Markedly elevated CPK levels, MRI findings, and muscle biopsy results are crucial for confirming the diagnosis. Despite being seronegative, the patient responded favorably to immunosuppressive therapy with corticosteroids and methotrexate. Prompt recognition and early initiation of immunosuppressive treatment are essential for achieving favorable clinical outcomes.

5. Limitations

- As it is a single patient observation, the finding cannot be generalized
- Lack of Electrophysiological studies that could strengthen the diagnosis
- Lack of long term follow up to look for presence of relapse, recurrence or long-term treatment effects

Conflict of Interest

The authors declare that they do not have any conflict of interest.

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